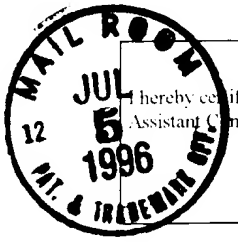
PATENT
Docket No. 204372000300



CERTIFICATE OF MAILING BY "FIRST CLASS MAIL"

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on July 1, 1996.

Joan R. Soll

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Lynn E. Spitler *et al.*

Serial No.: 08/105,444

Filing Date: August 11, 1993

For: PROSTATIC CANCER VACCINE

Examiner: P. Gambel

Group Art Unit: 1806

REPLY BRIEF

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is in response to the Examiner's Answer mailed 30 April 1996, relating to claims directed to anticancer vaccines containing a host prostate tissue antigen, which antigen is shared with a tumor inhabiting the host tissue but is overexpressed in tumor cells. The vaccine elicits an immune response against prostate tumor.

Appellants greatly appreciate the withdrawal of the rejection of the claims under 35 USC §103 as the Examiner has acknowledged that the art previously cited did not contain the suggestion to use prostate antigens in cancer therapy other than in relation to immunotoxins.

However, the Examiner's statement that "the newly cited art indicates that attempts to vaccinate against prostatic cancer with prostate-specific tissue was known at the time the invention was made; . . ." is inaccurate.

The two newly cited "references" were published in 1995 and are not available as prior art. Therefore, these two publications could not suggest Appellants invention "at the time the invention was made."

The Examiner has maintained three grounds of rejections, reflected in issues 1-3, in which the claims stand rejected under 35 USC §112. New arguments were raised and new art was cited to which appellants are entitled to respond. The examiner clarifies that the bases for rejection are not grounded in a lack of human clinical data, but rather an asserted failure to meet the criteria set forth in the "Forman factors." The remainder of this reply brief is concerned with showing that the standards implied by the Forman factors are met.[1]

It is believed that issues 1-3 should be resolved in favor of appellants for the following reasons.

Issue 1: Antitumor methods and vaccines

In the Examiner's Answer, page 7, this issue is summarized as "Rather the issue here is whether appellants' specification which provides no working examples enables any persons skilled in the art to use the full scope of claimed antitumor veterinary and human methods and vaccines which are so broad in scope that they contemplate and encompass every known and unknown overexpressed prostatic antigen or fragment thereof." The Examiner contends that he has set forth a sufficient case of nonenablement, in view of the standards provided in *Ex parte Forman*, to support this position.

---

[1] Although in the discussion of Issue number 1 of page 2 of the answer, the Examiner appears to refocus the argument on the Forman factors, page 4 of the Examiner's Answer appears to maintain an insistence on clinical results: "Pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable for the following reasons." Any putative requirement for *in vivo* clinical data has been squarely ruled as error by the holding in *In re Brana* 34 USPQ 2d 1436 (Fed. Cir. 1995).

Although characterized as failing to "adequately teach how to make and/or use the invention" the basis of the rejection is the Examiner's assertion of a lack of sufficient proof that the invention will operate as described. The Examiner appears to have taken the position that absent such data, it would require undue experimentation to practice the claimed invention.

The Examiner has agreed that the Office has a burden to make out a *prima facie* case, based on a preponderance of the evidence standard, that one of ordinary skill in the art would find the teachings insufficient to enable a claimed invention. The Examiner's case for the insufficiency of the disclosure (and hence undue experimentation required to practice the invention) is that Appellants have not met the standards as provided in *Ex parte Forman*, 230 U.S.P.Q.2d 546 (BPAI 1986) to demonstrate the efficacy of the antitumor vaccines of the presently claimed compositions and methods. The Examiner has relied on isolated passages taken from two publications, Hodge and Spitler, to assert that a *prima facie* case has been made out.

A. Enablement under the standards set forth in *Forman*

As recognized by the Examiner, one test that is commonly used to determine whether an invention is enabled is the standard set forth in *Ex parte Forman*. In *Forman*, the Board stated that factors that can be considered in determining whether an invention requires undue experimentation to practice include "1) the quantity of experimentation necessary, 2) the amount of guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of unpredictability of the art, and 8) the breadth of the claims." Applicants respectfully assert that in light of this standard, the specification is fully enabling. The following facts form the basis of this conclusion.

1. Amount of Experimentation

The focus of the amount of experimentation required is not the amount of experimentation that is required to practice every embodiment of a claimed invention but rather the amount of experimentation required to practice a single embodiment. For example, a large number of chemical patents that have issued in which there is a generic claim that reads on

thousands of members. Further, in *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988), the Court of Appeals for the Federal Circuit found that a claim that recited the use of any high affinity IgM was fully enabled despite the fact that the claim read on the use of nearly an infinite number of particular antibodies. In these cases, it would require an extremely enormous amount of effort to practice every embodiment, but only a minimal amount to practice any one embodiment. Patents such as these have not been rejected and have been upheld as being valid despite the enormous amount of experimentation that would be required to practice every embodiment of the claimed invention because only a minimal amount of experimentation is required to practice any particular embodiment.

In the present case, Appellants respectfully assert that although some experimentation is required to test a particular antigen that is overexpressed in prostrate tumors, such as PSA, in the claimed method or to generate a vaccine containing the antigen, such experimentation is routine and can be readily performed by a skilled artisan. In support of the routine nature of vaccine trials, Appellants have provided comments below directed to the cited Hodge and Spitler references in which numerous examples of anti-tumor vaccines and formulations are described.

2. The amount of guidance provided

Appellants respectfully assert that the specification provides sufficient guidance to practice the claimed invention without undue experimentation. At pages 10-12 of the specification, the preparation of antigens is described, at pages 12-13 the preparation of anti-id antibodies is described, at pages 13-15 the preparation of the vaccine formulation is described, and at pages 15-17 the administration of the vaccine is described. Clearly these passages provide the necessary guidance to practice the invention as presently claimed

3. The presence or absence of working examples

The Examiner has noted that the specification does not provide a working example. However, case law clearly holds that an application does not need to contain working examples. For example, see *Ex parte Krenzer*, 199 USPQ 227, 229 (PTO Bd. App. 1978) "a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation.";

Ex parte Nardi, 229 USPQ 79, 80 (BPAI 1986) "The fact that the specification is devoid of a working example is without significance."; and *De Nora v. Ives*, 209 USPQ 1121, 1127 (BPAI 1980) "The fact that the application does not incorporate a specific working example of that process is not determinative."

The specification clearly provides a description of specific vaccine formulations, namely vaccines containing PSA, PSMA, PAP, or anti-id antibodies thereto. The Examiner is correct in noting that specification does not contain data to demonstrate the efficacy of these vaccines in treating prostrate cancer but, as described below, a skilled artisan would reasonably expect that such vaccines would be efficacious as asserted.

4. The nature of the invention

The invention is in the field of cancer therapy, and in particular cancer vaccines. As noted in the Spitler article cited by the Examiner and discussed below, "Cancer vaccines have been used clinically since the turn of the century and continue to be widely used in cancer therapy." Therefore the invention is in a field that has been and is currently credible to practitioners.

5. The state of the prior art

The Examiner has cited Spitler, *Cancer Biotherapy* **10**:1-3 (1995) and Hodge *et al. International Journal of Cancer* **63**:231-237 (1995) as establishing that the art supports the Examiner's contention that undue experimentation is required to practice the claims. However, a fair reading of these publications confirms that they demonstrate the opposite.

a) Spitler

The Examiner has cited the first two sentences of Spitler as establishing that cancer vaccines do not work, but ignored the rest of the Spitler article and, indeed, the overall message it conveys. The sentences that begin the second paragraph state

> "Cancer vaccines have been used clinically since the turn of the century and continue to be widely used in cancer therapy. Nonetheless, despite this long history and wide use, there is no vaccine for therapy of

cancer which has been approved by a regulatory agency for marketing in this or any other country. The reason lies in the technology by which the products are produced. The cancer vaccines used up to the current decade have consisted of whole tumor cells or extracts of them combined with an adjuvant, most commonly bacille Calmette-Guerin, to enhance the immune response."

The article goes on to analogize the development of anticancer vaccines to the development of interferon as a therapeutic. As noted by Spitler, the problem heretofore encountered in use of anticancer vaccines has been attributable in large measure to the use of crude preparations, rather than identified and characterized antigens. The present invention, of course, uses such purified and characterized antigens.

At page 2 Spitler discloses "Cancer vaccines have finally reached the stage in technological development where commercial development can be envisioned." The reason given, consistent with the above, is that there a multiplicity of techniques available for purifying and characterizing individual antigens. Such a statement would not be made if undue experimentation were necessary in order to develop an antitumor vaccine.

On page 2 Spitler further discloses that

"Investigators working in the university setting using vaccines to treat cancer patients have occasionally seen clinical responses to this therapy, which at times has been dramatic. *Almost everyone working in this field has had the experience of seeing a dramatic regression of metastatic disease following vaccine therapy.* There are numerous published reports of these responses as well as unpublished observations of individual investigators." (Emphasis added)

Spitler continues by describing the response seen in one such patient that was treated with a melanoma cell vaccine, and then cites seven studies in which vaccines were successful vaccine

therapy has been seen in large series of patients. A copy of each of these cited studies that demonstrate the effectiveness of anticancer vaccines is attached hereto.

Spitler concludes by stating that

> "Now that the active components to the vaccine have been identified and purified, we are approaching the stage in technology where the interferons were at the beginning of the 1980s. The decade of the vaccine may finally have arrived!"

In summary, when read in its entirety Spitler does not support the Examiner's contention that the successful use of anti-tumor vaccines would not be credible to a skilled practitioner or that undue experimentation is required to practice the vaccines or methods of the present invention; Spitler's conclusion is exactly contra.

b) Hodge

The Examiner has cited Hodge as disclosing "that previous attempts to actively immunize patients with prostate adenocarcinoma cells admixed with adjutant showed little or no therapeutic benefit," citing page 31, column 1, first paragraph, but again ignores the remainder and, indeed, the main thrust of the article.

Line 5 of the second column on the same page states "Indeed, studies using *in vitro* immunization have shown the generation of CD4 and CD8 cells specific for PSA (Peace *et al.* 1994; Correale *et al.* 1995)."

The work reported in Hodge relates to a Rhesus monkey study showing that a recombinant *Vaccinia* virus that expresses human prostate-specific antigen (PSA) successfully generates a humoral and cellular immune response, without showing any toxicity. Specifically, at page 236 Hodge states "We have shown that it is possible to mount humoral and cellular immune responses specific for PSA in the Rhesus monkey after immunization with a recombinant vaccinia virus expressing PSA." (Also, see the title.) One skilled in the art reading Hodge would be left with the conclusion that 1) antitumor vaccines are viable therapeutics for

the treatment of cancers and 2) the PSA antigen is an attractive candidate for such therapeutic modalities.

In summary, the two references cited by the Examiner support appellants' position that a skilled artisan would not find the disclosure of antitumor vaccines as set forth in the specification in any way incredible, that many antitumor vaccines have been tested and that this demonstrates that it is well within the skill in the art and does not require undue experimentation to formulate an antitumor vaccine and verify its efficacy.

6. The relative skill of those in the art

The cited Spitler and Hodge publication establish the skill level of those in the relevant art is sufficient to make and use the invention vaccines without undue experimentation.

7. The predictability or unpredictability of the art

Predictability affects the amount of experimentation because, if something is predictable, then no experimentation is necessary, whereas if something in unpredictable, experimentation may be required. Appellants again refer to the Spitler article which indicates that the unpredictable nature of prior art vaccines lay in the inability to supply purified and characterized components. As this element has been removed (as it was for interferon) by virtue of the state of technology, the level of predictability has been enhanced. There is no reason to doubt appellant's statements that indigenous prostate antigens would be effective components of antiprostate cancer vaccines.

8. Breadth of the claims

The claims are commensurate in scope with the advances that the present application puts into the public domain. Specifically, the application advances the state of the art by disclosing anti-prostate vaccines that are based on antigens that are overexpressed in prostrate tumors and the present claims encompass vaccines and methods that are based on this advancement, e.g. contain the antigen, an expression system that generates the antigen *in situ*, or an anti-id antibody that mimics the antigen.

In summary, with regard to predictability, Spitler and Hodge clearly demonstrate that a skilled artisan does have an expectation of success in antitumor vaccines. Further, this expectation is heightened in the use of purified proteins or peptide fragments. Accordingly, the issue of whether a skilled artisan would accept appellant's claim of efficacy based on the present disclosure, is answered by the publications cited in the Examiner's Answer in the affirmative.

Issue 2. Scope of the active agent in the claimed vaccine and methods

The Examiner has stated that the claims 1-2, 4-8, 10-15, 17-22, 24-28, 30-35 and 37-40[2] are of such scope that "they contemplate and encompass every known and unknown overexpressed prostatic antigen or fragment thereof." The question here is whether there is any statutory bar that prevents an applicant from presenting claims that read on subject matter that is not yet known in the art when the applicant can outline the parameters that will characterize this subject matter and predict that it exists.

In *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988), the Court of Appeals for the Federal Circuit found that a claim to a method that utilizes a high affinity IgM monoclonal antibody were fully enabled. Such a claim reads on IgMs that had been generated and identified, as well as any IgM generated in the future that meets the affinity limitation. Similarly here it is legitimate for the claims to read on antigens that have not yet been identified, but which fit the limitations recognized by appellants as needed to be effective in the claimed methods and compositions.

---

[2] Claims 3, 9, 16, 23, 29 and 36 are free of this rejection.

The present invention resides in the recognition that a host prostrate tissue antigen, which antigen is shared with a tumor inhabiting the host tissue, and distinguishes immunologically the tissue from other types of normal tissue in the host can be used to elicit an immune response against prostate tumor. Three such antigens were known at the time of the present invention, namely PSA, PSMA, and PAP. Appellants do not claim to have identified or discovered these antigens or to have purified them to homogeneity, or manipulated them in any way other than to have described them as active ingredients in a vaccine. As appellants pointed out in their supplementary response to the final rejection, citing Wright, G.L. *et al.*, *Int J Cancer* (1991) **47**:717-725 and Beckett, M.L. *et al.*, *Cancer Res* (1991) **51**:1326-1333, additional antigens that are overexpressed in prostrate tumors have been described in the art which are distinguishable from PSA, PSMA and PAP. These publications show there is no reason to believe that all antigens which are characteristic of the prostate have been described. Since Appellants' invention does not relate to the discovery and description of these antigens, but rather to a method to use them once they are discovered, it would be unfair to limit the claims to those prostate-specific antigens that happen to be known at the time the present inventors' application was written or which had come to their attention at that time.

The Examiner has not walked through the steps utilized in testing a particular peptide, or peptide fragment for antigenicity in light of the *Forman* standard. The reason that this has not been done is that clearly the steps disclosed in the present application, as well as those known in the art, for testing a particular antigen for the "ability to elicit an immune response" are routine. Such steps involve 1) identifying the antigen/agent as being overexpressed in prostrate tumor relative to normal prostrate cells, 2) formulating the antigen in a suitable vaccine, and 3) testing the vaccine in an animal or human model. Although this type of experimentation may be time-consuming, it does not involve any inventive steps and relies only on art-known and routinely practiced technologies. Such methods can be practiced based on the teaching provided by appellants.

Because appellants' invention relates to a method to use members of the repertoire of prostate-characteristic antigens, it is improper to limit appellants only to those antigens whose

existence happens to coincide in time with the appellants' invention. Reversal of this basis for rejection is therefore requested.

Issue 3. Scope of the antigens, fragments and portions

The Examiner has clarified the rejection with regard to "fragments" and provided the same reasoning behind this rejection as was discussed above with regard to Issues 1 and 2. Appellants respectfully submit that under the *Forman* standards, it would not require undue experimentation to test any particular fragment of an overexpressed prostrate antigen for the ability to elicit an immune response. This can be accomplished using routine procedures. In addition guidance for the selection of the most promising fragment is provided by the availability of computer software at the time of the present invention that can identify potentially antigenic regions of a protein based on sequence information.

Since the Examiner has adduced no reasons, other than those adduced with respect to complete antigen that "immunologically effective portions" of antigens and antibodies would be ineffective, it is believed proper to include such portions within the scope of the present claims.

Conclusion and Request for Oral Hearing.

For the reasons stated above, Appellants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph for asserted lack of efficacy and asserted overbreathe be reversed and claims 1-40 passed to issue.

An oral hearing is requested.

The Assistant Commissioner is hereby authorized to charge any fees under 37 C.F.R. § 1.17 which may be required by this paper, or to credit any overpayment, to **Deposit Account No. 03-1952**. A duplicate copy of this sheet is enclosed.

Dated: July 1, 1996.

Respectfully submitted,

By: Kate H. Murashige

Kate H. Murashige
Registration No. 29,959

Morrison & Foerster
2000 Pennsylvania Avenue, N.W.
Washington, D.C. 20006-1888
Telephone: (202) 887-1533
Facsimile: (202) 887-0763